# Primary Adenoid Cystic Carcinoma of Head and Neck: Its Prognosis and Management - A Retrospective Analysis from a Tertiary Care Center

Subhalaxmi Rautray<sup>1</sup>, Tapan Kumar Sahoo<sup>2</sup>, Saroj Kumar Das<sup>2</sup>, Saroj Kumar Das Majumdar<sup>3</sup>, Dillip Kumar Parida<sup>4</sup>

<sup>1</sup>Assistant Professor, Department of Otorhinolaryngology, Sriram Chandra Bhanja Medical College, Cuttack, Odisha, India, <sup>2</sup>Senior Resident, Department of Radiation Oncology, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India, <sup>3</sup>Assistant Professor, Department of Radiation Oncology, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India, <sup>4</sup>Professor, Department of Radiation Oncology, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India

## **Abstract**

**Background:** Adenoid cystic carcinoma (ACC) is a rare malignant tumor of head and neck primary. It affects most commonly the major and minor salivary glands and rarely the paranasal sinuses, lacrimal gland, larynx, ear, vulva, etc. It is a slowly growing tumor, asymptomatic for a long period of time and usually presents with swelling and pain at the time of diagnosis. A wide radical resection of the tumor followed by radiotherapy is the main treatment modality.

Aim of the Study: To know the aggressiveness, diseases free interval and the prognosis of the ACC of head and neck.

**Materials and Methods:** Six cases of ACC of head and neck were taken. Three cases were having hard palate as the primary site, one case with nasopharynx as the primary site, one case with maxillary sinus, and one having the floor of mouth as the primary site. Cases were treated aggressively with surgery, adjuvant radiotherapy, palliative radiotherapy, and palliative chemotherapy (CT).

**Results:** Out of six cases, five cases were treated with surgery followed by radiotherapy. Four cases are now on regular follow-up without any disease recurrence or distant metastases. One case developed lung metastasis after 2-year of follow-up and is continuing palliative CT. One case presented with isolated temporal lobe metastasis and received radiotherapy to nasopharynx, its locoregional area and whole brain.

**Conclusion:** The behavior and survival status of ACC is not clear due to inefficient study data in literature. The study needs continuation with a more number of cases and longer duration of follow-up to draw significant data regarding disease-free interval and survival outcome of the diseases.

Key words: Adenoid cystic carcinoma, Head and neck primary, Management and prognosis

## INTRODUCTION

Adenoid cystic carcinoma (ACC) accounts for approximately 1% of all head and neck malignancies and 10-15 (22%) of all salivary gland neoplasms.<sup>1,2</sup> ACC is arises within glands, most commonly from major and minor salivary

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glands of the head and neck. The minor salivary glands of the oral cavity are the most common site.<sup>2</sup> It can occur also in the breast, trachea, paranasal sinuses, lacrimal glands, larynx, tracheobronchial tree, external ear, skin, and vulva and are known as non-salivary ACC.<sup>3</sup> ACC is a malignant tumor with benign histologic appearance. It is characterized by different histologic patterns, indolent, locally invasive growth with unpredictable clinical behavior, prolonged clinical course, and increased propensity for local recurrence and distant metastases.<sup>4</sup> Regional lymph node involvement occurs infrequently in ACC.<sup>5</sup> Aggressive surgical excision with adjunct radiotherapy is the required treatment modality.<sup>6</sup> Six patients of ACC of head and neck were taken in this study.

Corresponding Author: Tapan Kumar Sahoo, Department of Radiation Oncology, All India Institute of Medical Sciences, Bhubaneswar - 751 019, Odisha, India. Phone: +91-9437219525. E-mail: drtapankumars8@gmail.com

# **MATERIALS AND METHODS**

Six cases of ACC of head and neck were studied in between August 2013 and until date at All India Institute of Medical Sciences, Bhubaneswar, Odisha, India.

Out of 460 cases of head and neck cancers, only six cases (1.30%) were ACC. Five out of six cases presented at 30-50 years age group and one case presented in the age group of 60 years. Out of six cases, four cases are male and two cases are female. The oral cavity (hard palate and floor of the mouth) is the primary site of presentation in four cases. The nasopharynx and maxillary sinus as the primary site are seen in one case each. Pure cribriform type histology is seen in two hard palate cases and in one maxillary primary. Pure tubular, pure solid and mixed form seen in one cases each. All the six cases presented as locally advanced not less than T3 lesions and one case presented with isolated solitary temporal lobe brain metastasis. Three hard palate cases were treated with aggressive surgery (left extended maxillectomy with degloving approach) followed by adjuvant radiotherapy of 66 GY in 33 fractions to bilateral face and neck by CO60 in reduced portals after 45 GY. All the three cases are now on regular follow-up without any disease recurrence or distant metastases. One case of the floor of mouth primary underwent surgery (wide local excision + marginal mandibulectomy + bilateral modified neck dissections) with post-operative pathological staging of PT3N0MX with margin positivity and received adjuvant concurrent chemoradiation of 66 GY radiotherapy in 33 fractions along with weekly cisplatinum. After 2-year of follow-up, the patient developed bilateral lung metastasis and was treated with palliative chemotherapy (CT) with paclitaxel, cisplatin, and 5-flourouracil regimen up to six cycles with partial response, followed by oral tablet everolimus 10 mg once daily till date. The case with nasopharynx as the primary site found initially with isolated solitary temporal lobe metastasis was treated with palliative external beam radiotherapy (EBRT) to the brain of 30 GY in 10 fractions and local EBRT 66 GY in 33 fractions to bilateral face and neck. The ACC of maxillary sinus involved the inferior wall of orbit and was treated with surgery followed by EBRT of 66 GY in 33 fractions to bilateral face and neck and is now under regular follow-up since 26 months.

## **DISCUSSION**

According to the World Health Organization (2005), ACC is defined as "A basaloid tumor consisting of epithelial and myoepithelial cells in various morphological configurations, including tubular, cribriform, and solid patterns. It has a relentless clinical course and usually a fatal outcome." The

term ACC is still misleading as the tumor is not cystic.<sup>8-10</sup> The most cases arise in the minor salivary glands (60%). Palate, buccal region, maxilla, retromolar region, and lips are the common sites of involvement in the oral cavity.<sup>11</sup> The maxillary sinus ACC is the second most common sinonasal tumor.<sup>12</sup> and accounts for 10% of all sinonasal tract malignancies.<sup>13</sup> A recent review showed 74.3% of ACCs of the nasopharynx are presented at an advanced stage in the time of diagnosis.<sup>14</sup>

Gender predilection is an inconsistent feature in the literature. The peak age of incidence in ACC is 4<sup>th</sup> to 6<sup>th</sup> decades of life though cases have been reported in between ages of 10 and 96 years. <sup>15</sup> There are equal male and female distributions in ACCs. <sup>5</sup> Few data showed male predominance <sup>16</sup> in ACCs, whereas few showed female predominance. <sup>1</sup> Arsenic compounds, nickel, oak, or beech wood dust may be possible etiological factors. <sup>17</sup>

In this study, the majority were male, presented in the age group between 30 and 45 years, and hard palate as the primary. But, a large number of case studies are necessary for a significant data regarding the median age of presentation, incidence of the disease.

## Histopathology

ACCs are poorly encapsulated infiltrative lesions with grayish pink appearance. <sup>17</sup> The characteristic histopathologic features of ACC is proliferation of round or cuboidal cells with scarce cytoplasm and large, oval and hyperchromatic nuclei, and cells are arranged in the form of islands or sheets surrounded by abundant hyaline stroma exhibiting pseudocystic structures. <sup>18</sup> Microscopic examination of ACC comprises epithelial and myoepithelial cells. <sup>19</sup> ACC has a distinct histopathological appearance. Histopathologically, it has three main growth patterns: (1) Cribriform, (2) tubular, and (3) solid. <sup>19</sup>

Histologically, a mixture of patterns is common. Classification is based on the predominant pattern. Tumor with more than 30% of the solid pattern is classified as the solid variant, indicating its more aggressive behavior.

The tubular patterns are well differentiated or Grade I and is characterized by slender tubules, solid cords, and glandular structures infiltrating a well-hyalinized background. Cribriform pattern is the most common pattern, moderately differentiated or Grade II and is characterized by invasive tumor islands with multiple holes (pseudocysts or pseudolumina) punched out in a "Swiss cheese" or sieve-like pattern. The solid pattern is poorly differentiated or Grade III and consists of large islands of carcinoma composed predominantly of myoepithelial cells with infrequent true lumina, lined with cuboidal epithelial

cells, and occasional pseudocysts. Stroma is usually fibrous and extensive hyalinization can occur. Mitotic figures and apoptotic cells are commonly seen in the high-grade or solid pattern. Necrosis is seen only in the solid pattern, often centrally located within cell nests and appearing as a come do appearance. Mitotic figures and apoptotic cells are occasionally seen in the cribriform pattern. Perineural spread is commonly seen in all patterns. The tubular pattern has best prognosis, whereas cribriform pattern has intermediate and solid pattern has worst prognosis. To

In this study, out of six cases, three cases were a purely cribriform pattern, one with mixed tubular and cribriform pattern, one with the purely tubular pattern, one with purely solid pattern supporting the literatures.

#### **Presentation**

Most of the metastatic ACC remain asymptomatic for a long time.<sup>22</sup> Clinical signs and symptoms of ACC depend on the primary site and extent of the lesion. It can present as a painless slow-growing mass in the face or mouth.

Locally advanced tumors may invade nerves, causing paresthesia and paralysis. ACC has a tendency to infiltrate neural structures and to spread perineurally.

Intracranial involvement is rarely seen.<sup>3,23</sup> Tumors of the lacrimal gland may cause vision impairment and proptosis. ACC is the most common primary epithelial malignancy in the lacrimal glands.<sup>24</sup> ACC is the second most common primary tumor of the trachea with a poor prognosis. ACC of the larynx may present with hoarseness and difficulty in breathing.<sup>25</sup>

Maxillary sinus primary may present with nasal obstruction, epistaxis, nasal discharge, swelling, facial pain, paresthesia, etc., mimicking inflammatory conditions resulting in a late diagnosis of the disease. <sup>12,26</sup> ACCs have a prolonged natural history and slow growth even in local recurrence and distant metastatic situations. <sup>27</sup> There is a high propensity of ACC for perineural invasion and early hematogenous spread. <sup>28,29</sup> Brain involvement may occur by direct extension of tumor. <sup>17</sup> Regional metastases are seen in < 3% of cases,

Table 1: Demographic data with pre-treatment staging

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Age in years	Sex	Site of the primary lesion	Histopathological subtype	TNM stage	Stage	Distant metastasis at presentation
35	F	Right hard palate	Mixed cribriform and tubular type	CT4N0M0	Ш	No
45	M	Left hard palate	Cribriform type	CT4N0M0	Ш	No
30	M	Right sided nasopharynx	Tubular type	CT4N0M1	IV	Temporal lobe
42	M	Right sided floor of mouth	Solid type	CT3N1M0	II	No
40	F	Left maxillary sinus	Cribriform type	CT4N0M0	Ш	No
60	M	Left hard palate	None	CT3N0M0	Ш	No

Table 2: Radiological findings and treatment

Case number	CT/MRI findings	Initial treatment	FU in months	Recurrence/ metastasis	Palliative treatment
Case 1	MRI: Mass on the right maxilla involving adjacent soft palate and hard palate	EMDA (PT4N0MX)→EBRT of 66 GY in 33 fractions to bilateral face and neck	28	-	-
Case 2	MRI: Left paramedian hard palate lesion, involving left pterygoid plates, pterygoid muscles, pterygomaxillary fissure, maxillary antrum	EMDA (PT4N0MX)→EBRT of 66 GY in 33 fractions to bilateral face and neck	18	-	-
Case 3	CECT: Mass on right sided nasopharynx involving posterior nasal cavity causing obliteration of B/L nasopharyngeal airway, eustachean tube, torus tubaris and fossa of rosenmuller MRI: Metastasis in right temporal lobe	EBRT of 66 GY in 33 fractions to bilateral face and neck along with 30 GY in 10 fractions to whole brain	-	-	-
Case 4	MRI: Mass in right side floor of mouth involving anterior half of tongue, genioglossus, hyoglossus, geniohyoid muscles, mandible with right level IA, IB lymphadenopathy	WLE+mandibulectomy+MND PT4N0MX→concurrent CTRT of 66 Gy radiotherapy in 33 fractions along with weekly cisplatin	24	B/L lung metastasis	Palliative CT with paclitaxel+cisplatin→tablet everolimus
Case 5	CECT: Mass in the left maxillary sinus involving nasal septum, inferior wall of orbit	EMDA (PT4N0MX)→EBRT of 66 GY in 33 fractions to bilateral face and neck	26	-	-
Case 6	CECT: Mass in the left maxillary sinus eroding posterolateral wall involving hard palate, left side nasopharyngeal wall	EMDA (PT4N0MX)→EBRT of 66 GY in 33 fractions to bilateral face and neck	15	-	-

FU: Follow-up, EMDA: Extended maxillectomy with degloving approach, CTRT: Chemoradiation, B/L: Bilateral, CT: Chemotherapy, MRI: Magnetic resonance imaging, EBRT: External beam radiotherapy, WLE: Wide local excision, MND: Modified neck dissections

whereas distant metastases are comparatively common with the lung being the most common site followed by bones, liver, brain and omentum.<sup>30</sup>

The present study showed all the patients had T3 or T4 lesions, the majority with T4 lesions, one patient had distant metastasis as temporal lobe metastasis at initial presentation, and one had N1 disease clinico-radiological, but post-operative pathology showed PT4N0 with margin positive, the patient developed bilateral lung metastasis after 2 years of completion of treatment.

## **Prognosis**

ACC of minor salivary glands has worse prognosis than those of major salivary glands possibly due to more easy infiltration of the lesion of the minor salivary gland to extra glandular soft tissues and bone resulting increased dissemination of the tumour.<sup>5</sup> Solid histologic pattern, tumor size >4 cm, perineural invasion, delayed diagnosis, delayed treatment, surgical margin positive, recurrent local lesions, and distant metastases are associated with worse prognosis.<sup>5</sup>

## Management

ACC is found in younger age groups in comparison to squamous cell carcinoma and is relatively resistant to treatment. Tumor markers have no significant role in determining the prognosis. Treatment modalities depend on the stage of the tumor. It is difficult to prevent and predict the late local recurrence and distant metastases in ACC. There is no standard guideline for optimal treatment and outcome of the disease due to lack of prospective randomized multicentric trials. Surgical resection with possible widest margins with or without neck node dissection is the cornerstone of the treatment.<sup>31</sup> Neck node dissection depends on strong clinic-radiological suspicious of lymph node metastases. The majority cases present at an advanced stage during diagnosis and complete surgical resection remains difficult due to the larger size of the tumor and presence of nearby critical neurovascular structures.<sup>32</sup> Late diagnosis of ACCs contributes to poor prognosis of the disease.<sup>33</sup> Combination modality of treatment with surgery and radiotherapy is commonly required and results in better overall survival.<sup>16</sup> The tumor cells extend well beyond the clinical or radiographic margins and undergo perineural invasion and spread. Therefore, surgery requires excision with widest possible margins.<sup>5</sup> In maxillary sinus ACC, due to slow spread, late manifestations of the disease, and complex anatomy of the maxilla, complete surgical resection with widest margin is difficult. Rehabilitation options in huge maxillary defects still need further exploration.

ACCs are radiosensitive but not radio curable. Postoperative radiotherapy improves locoregional control and overall outcome. 31,34 A recent series data showed no difference in survival, the rate of recurrence, and time of recurrence between treatment with combination modality of surgery and radiotherapy or surgery alone.<sup>35</sup> In the case of inoperable/unresectable tumor and patient refusal for surgery, primary radiotherapy is recommended. The role of CT is not established as an effective modality of treatment for ACC.26 As prolonged survival is not unusual even after distant metastasis, CT should be best withheld in inoperable cases with local recurrence and distant metastasis until symptoms appear.<sup>36</sup> Clinical trials are going on for combination CT regimens treatment in local recurrent lesions or in distant metastases.<sup>37</sup> In ACC of head and neck, survival curve drastically declines at 10- and 15-year of survival even after combination treatment of surgery and radiotherapy.<sup>14</sup> Tumor growth rate and metastatic potential are independent tumor properties.<sup>38</sup> The 5-, 10-, and 15-year survival rates are 75%, 20%, and 10%, respectively.<sup>38</sup> 5-year overall survival for maxillary sinus primary is 62.9%.<sup>26</sup>

Five out of six cases in this study treated with surgical resection with possible widest margins, but one case showed post-operative margin positive and all the five cases received adjuvant radiotherapy (Tables 1 and 2).

## **CONCLUSION**

The combination of surgical resection and radiotherapy is the main modality of treatment. Complete surgical resection with widest possible margins is the cornerstone of treatment. The role of CT is not clear. ACCs of head and neck presented at an advanced stage (Stage III/IV) and complete surgical resection with clear margins is difficult due to late presentation, the larger size of tumor and nearby critical neurovascular structures. There is no clear data regarding prevention and prediction of local recurrence and distant metastases and it needs further clarification. This study needs continuation with more data and a longer period of follow-up to draw a possible survival outcome.

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